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ORIGINAL ARTICLE

Pyloric sphincter characteristics using EndoFLIP® in gastroparesis☆

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KEYWORDS
Gastroparesis;
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Diabetes

Abstract
Introduction and aims: Pyloric sphincter abnormalities may be detected in gastroparesis. Botulinum toxin A (BoNT/A) injection into the pylorus has been used to treat gastroparesis with varying results. The aim of the present article was to assess whether pyloric sphincter characteristics using the endoscopic functional lumen imaging probe (EndoFLIP®) with impedance planimetry in patients with gastroparesis correlated with symptoms, gastric emptying, and therapeutic response to pyloric sphincter BoNT/A injection.
Methods: EndoFLIP® study was performed on patients undergoing gastroparesis treatment with BoNT/A. The gastroparesis cardinal symptom index (GCSI) was applied prior to treatment and at post-treatment weeks 2, 4, 8, and 12.
Results: Forty-four patients were enrolled (30 with idiopathic gastroparesis, 14 with diabetic gastroparesis). Smaller pyloric diameter, cross-sectional area (CSA), and distensibility correlated with worse vomiting and retching severity at baseline. Greater gastric retention tended to correlate with decreased CSA and pyloric distensibility. BoNT/A treatment resulted in a significant decrease in the GCSI score at 2 and 4 weeks after treatment, but not at post-treatment weeks 8 or 12. Nausea, early satiety, postprandial fullness, and upper abdominal pain improved up to 12 weeks, whereas loss of appetite, stomach fullness, and stomach visibly larger improved only up to 4 weeks. Retching and vomiting failed to improve. Greater pyloric compliance at baseline correlated with greater improvement in early satiety and náusea at 8 weeks and greater pyloric distensibility correlated with improvement in upper abdominal pain.

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Conclusions: EndoFLIP® characteristics of the pylorus provided important pathophysiologic information in patients with gastroparesis, in relation to symptoms, gastric emptying, and predicting the response to treatment directed at the pylorus.

PALABRAS CLAVE
Gastroparesia;
EndoFLIP®;
Toxina botulínica tipo A;
Píloro;
Diabetes

Características del esfínter pilórico utilizando EndoFLIP® en gastroparesia

Resumen
Introducción y objetivos: Existen anormalidades en el esfínter pilórico que pueden ser detectadas en la gastroparesia. La inyección de toxina botulínica tipo A (BoNT/A) en el píloro ha sido utilizada en el tratamiento de gastroparesia con diversos resultados. El objetivo del presente artículo fue evaluar si existía correlación entre las características del esfínter pilórico observadas con el catéter luminal de imagen funcional (EndoFLIP®) con planimetría por impedancia en pacientes con gastroparesia, y síntomas, vaciamiento gástrico y respuesta terapéutica tras inyección de BoNT/A en esfínter pilórico.
Métodos: El estudio con EndoFLIP® se llevó a cabo en pacientes en tratamiento para gastroparesia con BoNT/A. Se utilizó el índice de síntoma cardinal de gastroparesia (GSCI por sus siglas en inglés) antes del tratamiento y a las 2, 4, 8 y 12 semanas después del tratamiento.
Resultados: Se reclutó a 44 pacientes (30 con gastroparesia idiopática, 14 con gastroparesia diabética). Se encontró correlación entre menor diámetro pilórico, área de sección transversal (AST) y distensibilidad, y vómito y arcadas más intensos en la evaluación basal. También se observó una tendencia a correlacionar de mayor retención gástrica con el AST y una distensibilidad pilórica disminuidas. El tratamiento con BoNT/A dio como resultado una disminución significativa en el GSCI a las 2 y 4 semanas después del tratamiento, pero no a las 8 o 12 semanas después. La náusea, la saciedad temprana, la plenitud posprandial y el dolor abdominal superior mejoraron hasta 12 semanas, mientras que la pérdida de apetito, la plenitud gástrica y el estómago visiblemente más grande mejoraron solo hasta 4 semanas. Las arcadas y el vómito no mejoraron. La elasticidad pilórica basal correlacionó con un mayor grado de mejora de saciedad temprana y náuseas a las 8 semanas, y la mayor distensibilidad pilórica correlacionó con una mejora en el dolor abdominal.
Conclusiones: Las características del píloro observadas con EndoFLIP® proporcionaron información fisiopatológica importante relacionada a síntomas, vaciamiento gástrico y predicción de respuesta a tratamiento dirigido al píloro en pacientes con gastroparesia.

Introduction and aims

Gastroparesis is a disorder with delayed gastric emptying in the absence of mechanical obstruction.[1] Gastroparesis generally has 3 etiologic types: diabetic, idiopathic, and postoperative. The symptoms of nausea, early satiety, and postprandial fullness that are attributed to gastroparesis correlate, albeit poorly, with delayed gastric emptying.[2,3]

Although antral hypomotility is associated with delayed gastric emptying,[4] it is the opening of the pyloric sphincter that ultimately enables gastric emptying to occur. The pylorus is a relatively understudied sphincter and its pathophysiology in gastroparesis is not well understood. Prior studies have analyzed pyloric sphincter pressure using water-perfused manometry,[5] high-resolution manometry,[6] and more recently, the endoscopic functional lumen imaging probe (EndoFLIP®, model EF325N, Crospon Ltd., Galway, Ireland).[7–9] Patients with diabetic gastroparesis were observed to have prolonged periods of increased pyloric tone and phasic contractions called ''pylorospasm''.[10] Some treatments for gastroparesis are aimed at the pylorus: botulinumtoxin A (BoNT/A) injections into the pylorus,[11,12] pyloroplasty/pyloromyotomy,[13] and pyloric stenting.[14] BoNT/A injection into the pylorus has been used to treat gastroparesis with varying results: somewhat favorable in open-label studies,[11,12,15,16] but not superior to placebo in controlled studies.[17,18] How to identify which patients may benefit from treatment to the pylorus is not clear.

EndoFLIP® is a technology that has been used to evaluate the lower esophageal sphincter (LES) in achalasia

and gastroesophageal reflux disease (GERD).[19–21] It is now utilized to aid in assessing the appropriate patients and in guiding surgical treatments of the LES, such as Nissen fundoplication for GERD and esophagomyotomy for achalasia.[22,23] EndoFLIP® uses a balloon with 16 sensors that is inflated inside a sphincter and evaluates its diameter, cross-sectional area (CSA), pressure, distensibility, and compliance. The use of EndoFLIP® in the pyloric sphincter is relatively novel. Through EndoFLIP® measurements, increased pressure and decreased compliance of the pyloric sphincter has been shown in patients with gastroparesis, compared with normal volunteers.[7]

The aim of the present study was to measure pyloric pressure, CSA, compliance, and distensibility using EndoFLIP® impedance planimetry in patients with gastroparesis. We chose patients with gastroparesis undergoing botulinum toxin injection to the pylorus for our proof-of-concept study to correlate pyloric sphincter characteristics with baseline symptoms, gastric emptying, and the response to pyloric sphincter BoNT/A injections.

Methods

Patients with known gastroparesis that were undergoing upper endoscopy for treatment with BoNT/A injection of the pylorus were asked to participate in the present analysis of the pyloric sphincter using EndoFLIP®. The Institutional Review Board of Temple University approved the study, and one of the researchers obtained written statements of informed consent from the patients. Prior to the procedure, the Patient Assessment of Upper GI Symptoms (PAGI-SYM) questionnaire,[24] which includes the Gastroparesis Cardinal Symptom Index (GCSI),[25] was filled out by each patient to evaluate the severity of their symptoms of gastroparesis.

Procedure

The patients fasted the night before the examination. Endoscopy was performed according to the standard clinical protocol at the Temple University Hospital Gastroenterology procedure unit. The patient was placed in the left lateral decubitus position and sedated with propofol using monitored anesthesia care. A large-diameter therapeutic upper endoscope (Olympus model GIF-1TH190) was orally inserted into the esophagus and then the stomach. Initial endoscopic examination was performed up to the antrum without traversing the pylorus. The EndoFLIP® catheter (Model EF325N, Crospon Ltd., Galway, Ireland) was then passed through the biopsy channel of the large-diameter therapeutic endoscope (to assist in passing the catheter into the pylorus), all under direct endoscopic visualization (fig. 1), as we have previously reported.[8]

With the EndoFLIP® balloon catheter in the pylorus, the balloon was inflated at a rate of 1cc/s up to 30 ml. The pylorus was assessed using EndoFLIP® balloon volume distensions at 30cc and then at 40cc. The pylorus was measured using the EndoFLIP® System model EF-100 with Revision software and the EndoFLIP® EF-325N catheter. Pressure was measured by the pressure transducer inside the balloon (fig. 2). The area (A) was measured using

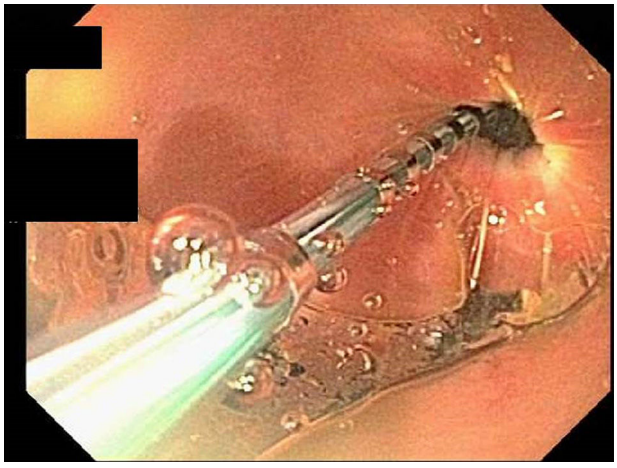

Figure 1 Endoscopic image of the pylorus during EndoFLIP®, showing catheter through the pylorus with 40 cc balloon distension.

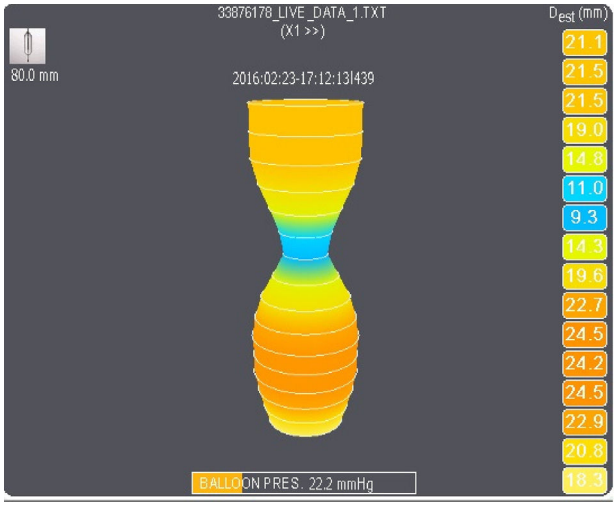

Figure 2 EndoFLIP® image of the pylorus at 40 cc balloon volume distension.

impedance planimetry, based on Ohm's Law, and the diameter was derived as the square root of $4A/\pi$. Distensibility was calculated as minimum CSA, divided by the pressure at each fill volume of the balloon. These measurements were assessed after the balloon was inflated at each balloon distension for a minimum of 5 seconds. Compliance and distensibility are related to the ability of the sphincter to stretch. Distensibility is calculated by taking the narrowest point of the sphincter, measuring its CSA, and dividing it by the pressure. It is a measure of how easily *the narrowest point* in the sphincter stretches. Compliance is calculated by taking the volume between 1 cm above and 1 cm below the narrowest point in the sphincter and dividing that volume by the distending pressure. Compliance provides information on the ease of stretching *within the whole sphincter* (2-cm long), and not just at one point (the minimum). Most reports in the literature use distensibility.

Once the EndoFLIP® assessment of the pylorus was completed, the catheter was withdrawn through the biopsy

channel. The pylorus was then intubated with the endoscope to complete the upper endoscopy, after which 200 units of BoNT/A (BOTOX®, Allergan plc, Dublin, Ireland) were injected circumferentially (5 injections of 40 u) into the pylorus.[11,12,18]

Follow-up assessments

The PAGI-SYM questionnaire was applied at follow-up at 2, 4, 8, and 12 weeks.[24] The Clinical Patient Grading Assessment Scale (CPGAS) was also applied at those follow-up visits, to evaluate the clinical response, graded by the patient, of the overall gastroparesis symptoms to treatment on a scale from 0 (no change) to 7 (completely better).[26,27] The prior gastric emptying test of the patient was reviewed.

Data analyses

Data were reported as counts and percentages for the categorical variables and mean ± SD (or median [range or quartile range]) for the continuous variables for overall gastroparesis patients, as well as by group (diabetic vs idiopathic). The Spearman correlation coefficient was employed to evaluate the association of the EndoFLIP® assessments at each fill volume of the balloon with the severity scores of the PAGI-SYM symptoms, GCSI, or gastric emptying results at baseline and/or the subsequent post-treatment improvements at the scheduled follow-up visits, in relation to overall gastroparesis, as well as to disease type, when appropriate. The effects of the BoNT/A injection treatment on the CPGAS, GCSI, and selected PAGI-SYM symptoms were reported using the score changes (follow-up score minus the baseline score) at weeks 2, 4, 8, and 12 of the follow-up visits. A change resulting in a negative number in the symptom score represented an improvement in symptoms. The Wilcoxon sign rank test was used to test whether there was a statistically significant improvement in any of the abovementioned measurements and the Fisher's exact test was used to compare a categorical variable between 2 patient groups (e.g., disease types). Multiple testing adjustments were not made, due to the exploratory nature of the study. P-values less than 0.05 were considered statistically significant. The SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) software was used for all the data analyses.

Results

Patients

Table 1 shows the demographic information of the 44 patients with known gastroparesis that underwent EndoFLIP® measurements of the pylorus and BoNT/A pyloric injections. Thirty-four (77%) of the patients were women and 10 (23%) were men. Patient mean ± SD age was 46.1 ± 13.3 years and BMI was 26.8 ± 6.6. Thirty (68%) patients had idiopathic gastroparesis, and 14 (32%) patients had diabetic gastroparesis.

EndoFLIP® assessments of pyloric sphincter at baseline

Figure 1 shows the endoscopic placement of the EndoFLIP® balloon catheter across the pyloric sphincter. Figure 2 shows sample displays of the recordings with inflation of the

Table 1 Demographic and disease characteristics of the gastroparesis patients at baseline (n = 44)*

	Total (n = 44)	Idiopathic[b] (n = 30)	Diabetic[a] (n = 14)
Female	34 (77%)	25 (83%)	9 (64%)
Male	10 (23%)	5 (17%)	5 (36%)
Age (years)	46.1 ± 13.3	42.7 ± 12.1	53.4 ± 13.0
BMI	26.8 ± 6.6	26.1 ± 6.6	28.3 ± 6.7
Predominant symptom			
Nausea	28 (63%)	22 (73%)	6 (43%)
Vomiting	13 (30%)	6 (20%)	7 (50%)
Abdominal pain	3 (7%)	2 (7%)	1 (7%)
GCSI	2.98 ±0.98	2.97 ± 0.88	3.00 ± 1.20
Nausea	3.73 ± 1.11	3.63 ± 1.19	3.93 ± 0.92
Vomiting	2.43 ± 1.84	2.03 ± 1.87	3.29 ± 1.49
Early satiety	3.93 ± 1.19	4.03 ± 1.16	3.71 ± 1.27
Postprandial fullness	3.98 ± 1.08	4.00 ± 0.95	3.92 ± 1.38
Upper abdominal pain	3.20 ± 1.66	3.20 ± 1.65	3.21 ± 1.76
Gastric emptying			
Retention % at 2 h	56.4 ± 18.1	57.6 ± 18.3	54.2 ± 18.3
Retention % at 4 h	33.0 ± 24.7	26.9 ± 21.6	44.2 ± 27.0

* Results expressed as mean ± SD for a continuous variable or count (%) for a categorical variable.
[a] One diabetic patient missing gastric emptying and postprandial fullness data.
[b] 6 idiopathic patients missing gastric emptying data.

Table 2 Patient EndoFLIP characteristics prior to treatment of gastroparesis (n = 44)*

	All patients	Idiopathic[a]	Diabetic
	(n = 44)	(n = 30)	(n = 14)
30 ml balloon inflation			
Diameter (mm)	8.9 ± 3.1	9.1 ± 2.6	8.5 ± 4.1
Cross-sectional area (mm^2)	76.6 ± 56.5	71.2 ± 39.3	88.3 ± 83.1
Pressure (mmHg)	17.4 ± 11.3	15.8 ± 10.8	20.7 ± 12.0
Distensibility (mm^2/mmHg)	7.8 ± 17.8	9.5 ± 21.3	4.3 ± 4.3
Compliance (mm^3/mmHg)	138.1 ± 142.	154.1 ± 155.3	106.1 ± 112.5
40 ml balloon inflation			
Diameter (mm)	11.0 ± 2.9	11.0 ± 2.6	11.1 ± 3.7
Cross-sectional area (mm^2)	102.6 ± 57.4	100.7 ± 46.2	106.7 ± 78.3
Pressure (mmHg)	22.3 ± 12.6	20.2±12.4	26.8 ± 12.3
Distensibility (mm^2/mmHg)	29.1 ± 93.9	40.3 ± 112.4	5.0 ± 4.8
Compliance (mm^3/mmHg)	165.4 ± 109.2	170.9 ± 110.4	153.8 ± 109.7

* Results expressed as mean ± SD for a continuous variable.
[a] 2 idiopathic patients missing compliance data.

EndoFLIP® balloon catheter. The pyloric sphincter measurements using EndoFLIP® are shown in Table 2. The pyloric sphincter contour was best seen at a balloon distension of 40cc. At that inflation volume, the measurements were: pyloric diameter 11.0 ± 2.9 mm, CSA 103 ± 57 mm^2, pressure 22.3 ± 12.6 mmHg, distensibility 29.1 ± 93.9 mm^2/mmHg, and compliance 165 ± 109 mm^3/mmHg. The EndoFLIP® measurements had a wide range. At a balloon distension of 30 cc the ranges were: pyloric diameters from 2.7 to 18.8 mm, pressures from 0 to 61.9, CSAs from 20 to 278, compliance from 15.5 to 800.6, and distensibility from 0.7 to 118.5. Low distensibility suggests a ''stiff'' pylorus, whereas high distensibility suggests an ''open'' or ''floppy'' pylorus. Of the 44 patients, 7 patients had pyloric distensibility ≥ 10 mm^2/mmHg (6 patients had idiopathic gastroparesis and 1 had diabetic gastroparesis). There were no statistically significant differences in pyloric sphincter characteristics between the patients with idiopathic gastroparesis versus diabetic gastroparesis (Table 2).

Gastric retention and correlations with EndoFLIP® at baseline

All patients in the present study had gastroparesis with delayed gastric emptying. The retention percentages at 2 h averaged 56.4 ± 18.1% (normal < 60%). The retention percentages at 4 h averaged 33.0 ± 24.7% (normal < 10%) (Table 1). Table 3 shows the correlations of gastric retention at 4 hours with the EndoFLIP® measurements. Gastric retention at 4 h tended to weakly correlate with distensibility with a negative r value, using both 30 cc and 40 cc inflations (n = 37; r = -0.28, p = 0.097 and r = -0.28, p = 0.099). Thus, decreased pyloric distensibility appeared to correlate with greater gastric retention at baseline. The correlation with distensibility with a negative r value was more prominent in the diabetic subgroup, using a 30-cc inflation (n = 13, r = -0.54, p = 0.06), but it did not reach statistical significance, possibly due to the small group size. Gastric retention at 4 h also tended to weakly and marginally correlate with pyloric CSA with a negative r value, using a 30-cc balloon inflation (n = 37, r = -0.28, p = 0.098). The correlation with CSA with a negative r value was more prominent in the diabetic subgroup (n = 13, r = -0.54, p = 0.054). Thus, a smaller pylorus was associated with increased gastric retention.

Table 3 Correlation of EndoFLIP measurements with gastric emptying (retention % at 4 h) at baseline*

	All patients	Idiopathic	Diabetic
	(n = 37)	(n = 24)	(n = 13)
30 ml balloon inflation			
Diameter	r = −0.27	r = −0.12	r = −0.35
	p = 0.11	p = 0.58	p = −0.24
Area	r = −0.28	r = −0.12	r = −0.54
	p = 0.10	p = 0.58	p = 0.05
Pressure	r = 0.07	r = 0.04	r = 0.03
	p = 0.67	p = 0.86	p = 0.93
Distensibility	r = −0.28	r = −0.12	r = −0.54
	p = 0.10	p = 0.58	p = 0.06
Compliance[a]	r = −0.24	r = −0.12	r = −0.35
	p = 0.16	p = 0.58	p = 0.24
40 ml balloon inflation			
Diameter	r = -−0.13	r = −0.16	r = 0.06
	p = 0.45	p = 0.45	p = 0.84
Area	r = −0.10	r = −0.10	r = 0.06
	p = 0.56	p = 0.65	p = 0.84
Pressure	r = 0.27	r = 0.22	r = 0.26
	p = 0.11	p = 0.30	p = 0.38
Distensibility	r = −0.28	r = −0.31	r = −0.10
	p = 0.10	p = 0.50	p = 0.74
Compliance	r = 0.03	r = 0.31	r = −0.42
	p = 0.87	p = 0.15	p = 0.15

* Results expressed as Spearman correlation coefficient (r) and p-value.
[a] 2 idiopathic patients missing compliance data at 30 ml, reducing the sample size n by 2.

Baseline symptom severity and correlations with EndoFLIP® at baseline

The PAGI-SYM was used to characterize gastroparesis symptom severity (Table 1). The severity of gastroparesis symptoms in descending order were: postprandial fullness (symptom severity of 4.0 ± 1.1), not being able to finish a normal-sized meal (3.9 ± 1.2), nausea (3.7 ± 1.1), loss of appetite (3.7 ± 1.3), stomach fullness (3.6 ± 1.3), bloating (3.5 ± 1.5), a visibly larger stomach (3.2 ± 1.6), upper abdominal pain (3.2 ± 1.7), vomiting (2.4 ± 1.8), and retching (2.3 ± 1.7).

Table 4 shows the correlations of several EndoFLIP® baseline measurements using 40 ml balloon inflation with selected PAGI-SYM symptoms at baseline. Smaller pyloric diameter and CSA with 40-cc inflation were correlated with increasing severity of vomiting (r = -0.30, p = 0.047 and r = -0.32, p = 0.04) and retching (r = -0.32, p = 0.03 and r = -0.35, p = 0.02). Pyloric distensibility tended to be associated with severity of vomiting (r = -0.28, p = 0.06) and retching (r = -0.29, p = 0.06) at baseline, with negative r values, i.e., less pyloric distensibility (stiffer pylorus) was associated with greater vomiting and retching severity.

Clinical response to botulinum toxin injections

There was improvement in overall gastroparesis symptoms after botulinum toxin injections of the pylorus at post-injection week 4, but it was not sustained at weeks 8 and 12 (Table 5).

The CPGAS score (mean ± SD), through which the patients graded their symptom improvement, was 3.34 ± 2.66 in overall gastroparesis improvement at 2 weeks ($p < 0.001$ versus 0 [no improvement]) and 2.57 ± 2.58 at 4 weeks ($p < 0.001$) but showed no improvement on average at 8 weeks (0.29 ± 2.55; $p > 0.10$) or 12 weeks (0.18 ± 0.46; $p > 0.10$). In the idiopathic gastroparesis group, the CPGAS score at 2 weeks was 3.30 ± 2.81, 2.30 ± 2.64 at 4 weeks, -0.33 ± 1.81 at 8 weeks, and 0.14 ± 0.35 at 12 weeks. In the diabetic gastroparesis group, the CPGAS score at 2 weeks was 3.43 ± 2.41, 3.14 ± 2.44 at 4 weeks, 1.36 ± 3.27 at 8 weeks, and 0.25 ± 0.62 at 12 weeks.

The CPGAS (responder >0) showed improvement in the overall gastroparesis symptoms at 4 weeks in 33 of the 44 patients (75%). The response at week 4 was similar between diabetic gastroparesis (10/14 = 71%) and idiopathic gastroparesis (23/30 = 77%, p = 0.72). However, the CGPAS response rate at week 8 was greater in diabetic gastroparesis (8/14 = 57%), compared with idiopathic gastroparesis (3/24 = 13%, p = 0.008).

The GCSI scores (mean ± SD) were significantly reduced at weeks 2 and 4 (2.01 ± 1.00, $p<0.001$ and 2.19 ± 0.94, $p<0.001$, respectively), compared with scores at baseline (2.98 ± 0.98) (Table 5). The GCSI scores had virtually returned to their baseline pretreatment values at post-treatment weeks 8 and 12.

BoNT/A injections produced a significant improvement in the symptoms of nausea, upper abdominal pain, early satiety, and postprandial fullness throughout the 12 weeks of follow-up, whereas significant improvement was achieved in the symptoms of belching, loss of appetite, stomach

Table 4 Correlation of EndoFLIP characteristics using 40 ml balloon inflation with selected symptom scores at baseline in all patients (n = 44)*

EndoFLIP characteristics	Nausea	Retching	Vomiting	Early satiety	Postprandial fullness	Loss of appetite	Upper abdominal pain
40 ml balloon inflation							
Diameter (mm)	r = -0.03 p = 0.86	r = -0.32 p = 0.03	r = -0.30 p = 0.047	r = 0.04 p = 0.80	r = 0.09 p = 0.56	r = 0.14 p = 0.36	r = 0.02 p = 0.90
CSA (mm^2)	r = -0.03 p = 0.86	r = -0.35 p = 0.02	r = -0.32 p = 0.04	r = 0.02 p = 0.91	r = 0.07 p = 0.64	r = 0.12 p = 0.42	r = -0.002 p = 0.99
Pressure (mmHg)	r = 0.09 p = 0.57	r = 0.18 p = 0.24	r = 0.15 p = 0.33	r = 0.15 p = 0.33	r = -0.04 p = 0.81	r = -0.04 p = 0.80	r = 0.11 p = 0.48
Distensibility (mm^2/mmHg)	r = -0.03 p = 0.84	r = -0.29 p = 0.06	r = -0.28 p = 0.06	r = 0.15 p = 0.32	r = 0.10 p = 0.54	r = 0.17 p = 0.28	r = -0.13 p = 0.40
Compliance (mm^3/mmHg)	r = 0.12 p = 0.46	r = -0.07 p = 0.65	r = -0.07 p = 0.65	r = 0.23 p = 0.14	r = 0.11 p = 0.48	r = 0.04 p = 0.80	r = -0.05 p = 0.73

*Results expressed as Spearman correlation coefficient (r) and p-value.

Table 5 Selected symptom scores at baseline and subsequent post-treatment changes*

	Baseline	wk 2	wk 4	wk 8	wk 12
	n = 44	n = 44	n = 44	n = 38	n = 34
CPGAS		3.34 ± 2.66 p < 0.001	2.57 ± 2.58 p < 0.001	0.29 ± 2.55 NS	0.18 ± 0.46 NS
GCSI	2.98 ± 0.98	2.01 ± 1.00 d = −0.97 ± 1.14 p < 0.001	2.19 ± 0.94 d = −0.79 ± 1.16 p < 0.001	2.96 ± 0.94 d = −0.02 ± 0.99 NS	3.18 ± 1.03 d = 0.16 ± 0.58 p = 0.08
Náuseas	3.73 ± 1.11	1.95 ± 1.29 d = −1.77 ± 1.44 p < 0.001	2.18 ± 1.26 d = −1.55 ± 1.45 p = 0.001	3.03 ± 1.37 d = −0.74 ± 1.43 p < 0.003	3.06 ± 1.63 d = −0.76 ± 1.35 p < 0.001
Retching	2.34 ± 1.67	1.75 ± 1.43 d = −0.59 ± 1.92 p = 0.04	2.00 ± 1.28 d = −0.34 ± 1.93 NS	2.79 ± 1.40 d = 0.55 ± 1.78 p = 0.07	3.50 ± 1.21 d = 1.24 ± 1.89 p < 0.001
Vomiting	2.43 ± 1.84	1.84 ± 1.61 d = −0.59 ± 2.30 p = 0.08	2.27 ± 1.39 d = −0.16 ± 2.17 NS	2.79 ± 1.56 d = 0.32 ± 2.22 NS	2.94 ± 1.70 d = 0.47 ± 1.83 NS
Stomach Fullness	3.55 ± 1.28	1.95 ± 1.18 d = −1.59 ± 1.76 p < 0.001	2.45 ± 1.09 d = −1.09 ± 1.79 p < 0.001	2.74 ± 1.35 d = −0.84 ± 1.62 p = 0.002	3.00 ± 1.44 d = −0.53 ± 1.66 p = 0.09
Early satiety	3.93 ± 1.19	2.25 ± 1.43 d = −1.68 ± 1.74 p < 0.001	2.41 ± 1.34 d = −1.52 ± 1.65 p < 0.001	3.24 ± 1.26 d = −0.66 ± 1.42 p = 0.004	3.06 ± 1.37 d = −0.94 ± 1.23 p < 0.001
Postprandial fullness[a]	3.98 ± 1.08	2.25 ± 1.50 d = −1.74 ± 1.90 p < 0.001	2.48 ± 1.34 d = −1.51 ± 1.56 p < 0.001	3.16 ± 1.24 d = −0.78 ± 1.64 p = 0.005	2.74 ± 1.56 d = −1.21 ± 1.71 p < 0.001
Loss of appetite	3.66 ± 1.27	2.45 ± 1.39 d = −1.20 ± 1.64 p < 0.001	2.34 ± 1.18 d = −1.32 ± 1.52 p < 0.001	2.87 ± 1.30 d = −0.68 ± 1.82 p = 0.03	3.4 4 ± 1.13 d = −0.15 ± 1.33 NS
Bloating	3.45 ± 1.52	2.00 ± 1.29 d = −1.45 ± 1.62 p < 0.001	1.77 ± 1.33 d = −1.68 ± 1.76 p < 0.001	3 .01 ± 1.34 d = −0.37 ± 1.67 NS	3.41 ± 1.31 d = −0.09 ± 1.68 NS
Stomach visibly larger	3.18 ± 1.60	1.91 ± 1.44 d = −1.27 ± 1.65 p < 0.001	2.20 ± 1.52 d = −0.98 ± 1.73 p < 0.001	2.95 ± 1.39 d = −0.32 ± 1.25 NS	3.21 ± 1.59 d = −0.12 ± 0.95 NS
Upper abdominal pain	3.20 ± 1.66	2.02 ± 1.30 d = −1.18±2.14 p < 0.001	2.18 ± 1.39 d = −1.02±1.95 p = 0.001	2.61 ± 1.31 d = −0.63±1.81 p = 0.05	2.59 ± 1.44 d = −0.59±1.46 p = 0.03

* Results reported as mean ± SD, with the change from baseline (d) and the associated p-value for mean change = 0.
[a] One patient missing baseline postprandial fullness data, reducing all the related ns by 1. NS: p > 0.10.

fullness, and a visibly larger stomach only up to 4 weeks and was not sustained at 12 weeks (Table 5). BoNT/A injections failed to improve symptoms of vomiting and retching. Retching was worse at week 12 of follow-up, compared with the baseline values (a 1.2 ± 1.9 difference).

Clinical response and correlations with EndoFLIP®

We correlated the score changes (week 8-baseline) in symptom severity 8 weeks after pyloric BoNT/A injection with the EndoFLIP® characteristics prior to injection to assess predictors for a sustained (2-month) response (Table 6). Pyloric compliance using the 40-cc inflation prior to botulinum toxin treatment was associated with improvement in nausea (r = -0.34, p = 0.03) and early satiety (r = -0.34, p = 0.04) at 8 weeks, with negative r values. Thus, a larger pyloric compliance at baseline was correlated with a greater improvement in early satiety and nausea with BoNT/A treatment at 8 weeks. Baseline pyloric distensibility was related to improvement in upper abdominal pain (r = -0.38, p = 0.02), with a negative r value, i.e., a bigger baseline pyloric distensibility was related to a greater improvement in upper abdominal pain at 8 weeks. Larger pyloric diameter and area at baseline appeared to be related to worsening in retching with botulinum treatment (r = 0.31; p = 0.06 and r = 0.34; p = 0.03). Those relationships of improvement in symptoms with baseline EndoFLIP® parameters were present in one or both of the subgroups, as well (data not shown). For instance, in the patients with idiopathic gastroparesis (n = 24), a larger baseline pyloric compliance was related to a greater improvement in nausea (r = -0.41, p = 0.046) and in early satiety (r = -0.39, p = 0.06) at 8 weeks after treatment. In addition, a greater baseline pyloric distensibility

Table 6 Correlation of EndoFLIP characteristics with improvement of selected symptom scores at 8 weeks (8 week score-baseline) in all patients with follow-up data (n = 38)*

	Nausea	Retching	Vomiting	Early satiety	Postprandial fullness[a]	Upper abdominal pain
40 ml inflation						
Diameter	r = −0.18	r = 0.31	r = 0.001	r = −0.20	r = −0.19	r = −0.32
	p = 0.27	p = 0.06	p = 1.00	p = 0.23	p = 0.25	p = 0.05
Area	r = −0.19	r = 0.34	r = 0.01	r = −0.16	r = −0.16	r = −0.29
	p = 0.26	p = 0.03	p = 0.94	p = 0.33	p = 0.33	p = 0.07
Pressure	r = 0.17	r = −0.03	r = −0.19	r = 0.17	r = 0.08	r = 0.26
	p = 0.31	p = 0.86	p = 0.26	p = 0.30	p = 0.63	p = 0.12
Distensibility	r = −.25	r = 0.21	r = 0.10	r = −0.24	r = −0.14	r = −0.38
	p = 0.12	p = 0.21	p = 0.53	p = 0.14	p = 0.42	p = 0.02
Compliance	r = −0.34	r = −0.02	r = −0.04	r = −0.34	r = −0.22	r = −0.05
	p = 0.03	p = 0.92	p = 0.82	p = 0.04	p = 0.19	p = 0.77

* Results expressed as Spearman correlation coefficient (r) and p-value.
[a] 1 idiopathic patient missing baseline postprandial fullness data, reducing the related sample size by 1.

was marginally related to a greater improvement in upper abdominal pain (r = -0.36, p = 0.08). In the diabetic patients (n = 14), a larger pyloric diameter and area using 40-cc balloon inflation were associated with better improvement in upper abdominal pain (r = -0.60, p = 0.02 and r = -0.59, p = 0.03, respectively) at 8 weeks (Table 6).

Discussion and conclusions

Gastroparesis is a difficult disorder to treat and it is not known why some patients respond to certain therapies and others do not. More recently, treatments for gastroparesis are being directed at the pylorus, albeit with varying results. Impedance planimetry with EndoFLIP® to characterize pyloric pathophysiology in patients undergoing treatment of gastroparesis was the core of this study. We wanted to assess whether pyloric pathophysiology was related to symptoms and gastric emptying, and whether it could help predict which patients might respond to therapy directed at the pyloric sphincter. Botulinum toxin injection was used for that therapy in our proof-of-concept study. Gastric retention at 4 hours tended to correlate negatively with cross-sectional area and pyloric distensibility, with negative r values. Pyloric diameter, CSA, and distensibility were associated with the symptom severity of retching and vomiting. In other words, the symptoms of retching and vomiting were more severe, the smaller the pylorus and the stiffer the pylorus.

In the present study, BoNT/A injection into the pylorus mainly improved the symptoms of nausea, early satiety, postprandial fullness, and upper abdominal pain over the course of 4-12 weeks, but the symptoms of retching and vomiting failed to improve. Interestingly, a larger pyloric diameter and area at baseline appeared to be related to worsening in retching with botulinum treatment. Greater pyloric compliance at baseline was related to better improvement in nausea and early satiety. Gourcerol et al. found that pyloric dilation in gastroparesis patients with low pyloric compliance improved their gastric symptoms.[7]

The EndoFLIP® parameters obtained in our gastroparesis patients were remarkably similar to those obtained in the study by Gourcerol et al.,[7] which showed that pyloric distensibility was 25.2 ± 2.5 mm^2/mmHg in normal subjects. Distensibility was abnormal if it was below 10 mm^2/mmHg. That study assessed gastric emptying with breath testing, whereas in our study, gastric emptying was assessed through scintigraphy.

Our study suggests that pyloric characteristics assessed by EndoFLIP® may provide measures that are helpful for predicting gastroparesis symptom response to therapies directed at the pylorus. In this proof-of-concept study, we employed botulinum toxin injection into the pylorus. BoNT/A injection into the pylorus has been used to treat gastroparesis with varying results: somewhat favorable in open-label studies,[9,10,13,14] but not superior to placebo in controlled studies.[15,16] We found that botulinum toxin treatment resulted in a decrease in the gastroparesis symptoms assessed through the GCSI at weeks 2 and 4 after treatment, but that decrease was not sustained at 8 and 12 weeks after injection. Thus, in agreement with the guidelines on gastroparesis,[1] treatment with botulinum toxin is not a long-term treatment option for many of those patients.

Among the limitations of the present study was the fact that all patients were treated with BoNT/A injection of the pylorus; we did not have a sham treatment control group. Likewise, we did not study normal subjects with the EndoFLIP®, which was done in a previous study by Gourcerol et al.[7] However, we did demonstrate objective parameters of the pylorus assessed through EndoFLIP® and correlated them with symptoms, gastric emptying, and improvement in symptoms. The EndoFLIP® measurements were performed under propofol anesthesia, which could potentially affect pyloric tone and contractility. Our single site study cohort included 44 patients, which might have limited some of the statistical relationships, especially those in which the subgroups of diabetic gastroparesis and idiopathic gastroparesis were analyzed. Other limitations include the absence of follow-up EndoFLIP® and gastric emptying study after BoNT/A treatment, the unblinded study

design, and possible under-powering of the study for further subgroup analysis.

In conclusion, the present study showed that impedance planimetry of the pylorus using EndoFLIP® provided important pathophysiologic information in patients with gastroparesis in relation to symptoms, gastric emptying, and response to treatments directed at the pylorus. Pyloric area and distensibility correlated with gastric retention, as well as with symptoms of retching and vomiting. BoNT/A improved symptoms of nausea, early satiety, postprandial fullness, and upper abdominal pain. Pyloric compliance correlated with improvement in symptoms of early satiety and nausea. Therefore, EndoFLIP®, primarily with 40-cc balloon distension, may provide important pathophysiologic information on the pylorus in patients with gastroparesis. Such information may help improve our understanding of pyloric function and aid in identifying those patients that could benefit from pyloric-directed therapies. Our study was specifically related to the use of EndoFLIP® in predicting the response to intrapyloric BoNT/A injection. Further studies are needed to evaluate the pylorus in patients with other causes of gastroparesis and to study how the pylorus responds to different treatments, such as pyloromyotomy.

Author contributions

Mohammed Saadi, MD: study concept and design; data entry; analysis and interpretation of data; statistical analysis, drafting of manuscript

Daohai Yu, PhD: study design; analysis and interpretation of data; statistical analysis, critical revision of the manuscript for important intellectual content

Zubair Malik, MD: study concept and design, critical revision of the manuscript for important intellectual content

Henry P. Parkman, MD: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; study supervision

Ron Schey, MD: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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